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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: **Binie V. Lipps** **Frederick W. Lipps**	§ § § §	ATTY DCKT NO: FWLPAT015US
Serial No.: 10/047,945	§ §	Art Unit: 1644
Filed: January 14, 2002	§ §	Examiner: Szperka, Michael Edward
For: DIAGNOSIS AND TREATMENT FOR IMMUNOGLOBULIN E (IgE) IMPLICATED DISORDERS	§ § §	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL

Submitted herewith concerning the subject patent application, please find enclosed:

(1) Appellant's Brief on Appeal (14 pages, in triplicate)

(2) a check for $250.00, to cover the fee seen due for filing a brief in support of appeal. Applicant is entitled to and asserts small entity status.

Respectfully submitted:

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I hereby certify that this correspondence and all documents referred to herein is being deposited with the United States Postal Service as first class mail in an envelope addressed to the above addressee on
20 October 2005

10-20-05
by John R. Casperson, Reg. No. 28,198 (date)

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APPELLANT'S BRIEF ON APPEAL

This brief is in furtherance of the Notice of Appeal filed in this case on August 30, 2005.

The fees required under 37 CFR 1.17 (c) and any required petition for extension of time for filing this brief and fees therefor are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

This brief is transmitted in triplicate.

REAL PARTY IN INTEREST

The real party in interest is Binie V. Lipps.

RELATED APPEALS AND INTERFERENCES

With respect to other appeals or interferences that will directly affect, or be directly affected by, or have a bearing on the Board's decision in this appeal: There are no such appeals or interferences

STATUS OF CLAIMS

A. TOTAL NUMBER OF CLAIMS IN APPLICATION: 18

Claims in the application are: 1-18

B. STATUS OF ALL THE CLAIMS

1. Claims cancelled: None
2. Claims withdrawn from consideration but not cancelled: 1-8
3. Claims objected to: None
4 Claims allowed or confirmed: None
5. Claims rejected: 9-18

C. CLAIMS ON APPEAL

The claims on appeal are: 9-18

Claims 9-18 are on appeal and are reproduced in the Appendix.

STATUS OF AMENDMENTS

All amendments have been entered and the claims are reproduced in the appendix as so amended.

SUMMARY OF CLAIMED SUBJECT MATTER

Reference to the drawing is not required for an understanding of the invention.

IgE antibody is a blood component that is generated in the body as part of the immune response. In some people, it is known that reducing free IgE levels can alleviate disease symptoms. Xolair(R) (Omalizumab), a monoclonal antibody which functions by targeting IgE antibody, for example, was approved by the FDA in June 2003 for treatment of persistent asthma and is being evaluated in other IgE-mediated diseases. It is for subcutaneous use. (see Exhibit 1, which is presented as argument). See also specification, page 4, lines 1-6 and page 4, line 26 through page 5, line 5.

The inventors discovered that a genus of peptides can be used to reduce free IgE levels in humans. The selected peptide can be administered orally. (Page 6, lines 16-20). The genus is described as a peptide containing at least the first four amino acids from the N-terminal of the sequence Leu Lys Ala Met Asp Pro Thr Pro Pro Leu Trp Ile Lys Thr Glu. (page 7, lines 8-11, also original claim 9).

Generally speaking, in the range of from about 0.02 to about 200 milligrams of the peptide is orally administered on a daily basis, usually in the range of from about 0.2 to about 20 milligrams on a daily basis. The peptide is administered to humans having an elevated serum IgE level, as compared to norms. Often, a patient having an elevated IgE level will also have an elevated NGF, Insulin, Myoglobin and/or ADA serum level. (page 7 line 23-page 8 line 3, see also Table 1 appearing on page 11 and Table 2 appearing on page 12)

Representative species of the claimed genus of peptides are disclosed as
SEQ ID NO 2: Leu Lys Ala Met Asp Pro Thr Pro Pro Leu Trp Ile Lys Thr Glu
SEQ ID NO 4: Leu Lys Ala Met Asp Pro Thr Pro Pro Leu Trp Ile
SEQ ID NO 5: Leu Lys Ala Met Asp Pro Thr Pro Pro Leu Trp

SEQ ID NO 1: Leu Lys Ala Met Asp Pro Thr Pro Pro Leu

SEQ ID NO 6: Leu Lys Ala Met Asp Pro Thr Pro Pro

SEQ ID NO 7: Leu Lys Ala Met Asp Pro Thr Pro

SEQ ID NO 3: Leu Lys Ala Met Asp

(specification, sequence list)

Most of the data in the specification is based on the species set forth above as SEQ ID NO: 1, referred to as LT-10 (for ten amino acids) in the specification. However, the specification states that all three versions that were made, LT-15, LT-10 and LT-5 have similar biological activity and are useful in this invention as are the peptides of intermediate length (page 3, lines 23-25). LT is an acronym for Lethal Toxin neutralizing factor, which is what the inventors named the class of peptides in their earlier work (US 5,576,297 and US 5,744,449, incorporated by reference, specification, page 5, lines 13-16). How to make the peptides is well known in the art as evidenced by the referenced patents, for example.

The specification in a working example from page 9 line 13 through page 13 line 2 demonstrates that IgE and other serum proteins can be assayed from saliva and teaches how to do it. Formulating the necessary antibodies is well within the skill level in the art. The specification in a working example at page 8, lines 11-23 demonstrates that LT-10 binds IgE when mixed with saliva *in vitro*. The specification, in another working example using the procedure described at page 13 lines 3-22 shows in Table 4 appearing on page 15 that LT-10 treatment of a human *in vivo* reduced free serum IgE as measured in saliva. In Tables 3 - 7, Experiment 3 (Expt #3) is the column showing the effect of LT-10 treatment on various blood proteins. Table 5 appearing on page 16 further shows it also reduced NGF, and Table 6 appearing on page 17 still further shows it also reduced insulin. These test results are also summarized in the Figure. The specification also shows correlation between elevated IgE and other blood protein levels with various disorders and diseases (Tables 1 and 2 appearing on pages 11-12).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 9-18 stand rejected solely under 35 USC 112, first paragraph, as failing to comply with the enablement requirement.

ARGUMENT

MPEP 2164 discusses the enablement requirement. The factors to be considered are (A) The breadth of the claims (B) The nature of the invention (C) The state of the prior art (D) The level of one of ordinary skill (E) The level of predictability in the art (F) The amount of direction provided by the inventor (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. All of the factors have to be considered. (MPEP 2164.01(a)). Neither Office Action lists these factors nor attempts to address any of them in any systematic way. Instead, both office actions focus almost exclusively on the credibility of the working examples.

The nonenablement rejection as discussed in the office actions is summarized as follows. The full text of certain paragraphs (with emphasis added) is shown in the end notes.

First Office Action dated January 24, 2005

page 5,	first paragraph: quotes 35 USC 112
	second paragraph: states that claims 9-18 are rejected for nonenablement
	third paragraph: discuss state of the art vis. a vis. the peptides
page 6,	first full paragraph, contests causation between IgE levels and diseases[1]
	second paragraph, contests whether the peptide binds to the IgE[2]
page 7	first full paragraph, contests the validity of the working examples, concludes data was due to random chance[3]
	second paragraph, contests the validity of the working examples, concludes undue experimentation required[4]
page 8	first full paragraph, contests the diagnosis step of claims 17-18

second paragraph, concludes undue experimentation required for claims 17-18

In response to the first office action, the claims were amended to their present form.

Final Office Action dated June 28, 2005

Paragraph 7: quotes 35 USC 112

Paragraph 8: states the rejection of claims 9-18, incorporates the reasoning in the earlier office action

page 4, first paragraph: paraphrases portions of applicant's earlier response

second paragraph: contests the utility of claim 9 as amended[5]

page 5 first full paragraph: contests the working examples based on lack of statistical proof, lack of a theory of operability, in vivo data, procedures used, failure to perform repeat experiments[6]

page 6 first full paragraph: concludes applicant has failed to provide "any evidence which indicates that the data disclosed by Applicant is due to anything more than random chance" and that the skilled artisan would not be able to perform the claimed method without undue experimentation

This appeal is taken in response.

The present fact situation is similar to In re Wands, 8 USPQ2d 1400 (Fed Cir. 1988), which is believed controlling as to the analysis required. In Wands, the court noted that there was no disagreement as to the facts, but merely a disagreement as to the interpretation of the data and the conclusion to be made from the facts. The court warned that it would be improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the other factors. That is what the examiner has done in this case.

The breadth of the claims

The examiner did review the scope of claims 17 and 18 in the first office action, but has failed to

otherwise discuss the claim language in either office action. Many of the arguments in the end notes address binding, correlations between IgE levels and disease, and antibodies, which simply have no bearing on claim 9 on appeal.

The nature of the invention

The characterizations of the invention by the examiner have not been made with reference to the claims. As claimed, this is conceptually a really simple invention. Administer an effective amount of X to to accomplish Y. Then the specification should have been reviewed to determine whether it teaches how to do this. The examiner failed to do this.

The state of the prior art

The prior art teaches only free-IgE reduction with full blown antibodies. Free-IgE reduction with a peptide is not known. The examiner therefore argues that applicant's assertion is not credible. However, "The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." Gould v. Quigg, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987)

The level of one of ordinary skill

The level of skill in the art is high. Most likely an MD or a Ph.D. in Biochemistry with several years experience. Individuals of such skill know how to synthesize antibodies and peptides, how to test these materials for effectiveness, and how to measure serum protein levels. This factor was not addressed in either office action..

The level of predictability in the art

Peptides which have the same active domain probably all will work. The specification states that LT-15, LT-10 and LT-5 all have similar biological activity and are useful in this invention as are the peptides of intermediate length. This factor was not addressed in either office action.

The amount of direction provided by the inventor

The specification identifies the peptides. The specification teaches how to use the peptides to reduce free IgE levels. The specification teaches how to measure IgE levels from saliva. All of this was ignored by the Examiner in both office actions.

The existence of working examples

The specification shows free IgE reduction in saliva treated with the 10 amino acid peptide. The specification shows free IgE reduction in a human treated with the peptide, as measured in saliva. All of this was dismissed by the Examiner as lacking credibility for want of statistical validation and explanation of a theory of mechanism.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

None. The additional runs demanded by the examiner are not further experimentation, they are practicing the invention. No attempt has been made by the examiner to quantify just what is needed and whether that amount would constitute undue experimentation.

Whether or not the data is believable or credible is a utility issue, not an enablement issue. However, the examiner has refrained from giving a utility rejection, probably because he knows it will not stand up. In *In re Langer* 183 U.S.P.Q. 288 (C.C.P.A. 1974) the Court of Customs and Patent Appeals discussed utility and operability under 35 USC 101:

> "As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented **must** be taken as sufficient to satisfy the utility requirement of section 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope" (emphasis added).

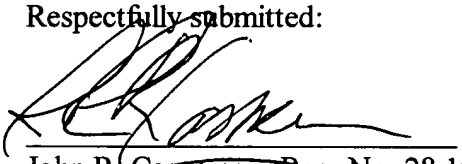
The examiner essentially argues that applicant's data is not credible because it has not been shown to be statistically supported. However, what the examiner overlooks is that what is presented is

human clinical data. The only way to statistically verify its validity is by providing more human clinical data. And that, in essence, is a requirement for human clinical trials which is clearly outside of the law. See MPEP 2107.03 and the cases cited therein.

CONCLUSION

In view of the forgoing arguments, reversal of all grounds of rejection is requested.

Respectfully submitted:



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END NOTES

[1] "Applicant has asserted that the metalloproteinase inhibiting peptide of SEQ ID NO: 1 can be used to reduce the levels of various serum proteins and treat numerous diseases. Specifically, applicant has asserted that administration of SEQ ID: 1 decreases IgE level, and that numerous disorders including diabetes, depression and autoimmunity are caused by high levels of IgE (see particularly Table 1, table 2, and the paragraph that spans pages 12 and 13). **High levels of IgE are not recognized in the art as being correlated with diseases such as diabetes and depression**, and as such high levels of IgE are certainly not recognized as causing said diseases (The Merck Manual, seventeenth edition, 1999, see particularly pages 165-177 and pages 1531-1538). The data presented in Tables 1 and 2 is not convincing to a person of skill in the art that a correlation, let alone a casual relationship, exists between IgE levels and the indicated diseases because **no statistical measurements were performed to demonstrate that the observed results were not due to random chance.** The influence of random chance is quite high given that only one individual was measured in both diabetes and depression (note that the pooled diabetic sample is not meaningful since it contains material from just two individuals and a high value from one of the samples would mask a low value in the other sample). **No indication is given that experiments such as those in Tables 1 and 2 were ever repeated or that they are reproducible.**"

[2] "Support for the IgE reducing properties of the SEQ ID NO: 1 peptide can be found in the specification on page 8, lines 11-23. No data concerning these experiments is provided, so it is not clear how applicant has determined that the peptide of SEQ ID NO: 1 binds to the IgE, although it appears that applicant's failure to detect IgE in samples treated with the peptides of SEQ ID NO: 1 has lead to this conclusion (see particularly page 8, lines 14-17 and I21-23). As stated earlier, SEQ ID NO: 1 is a metalloproteinase inhibitor. It is not an enzyme, so it could not have degraded the IgE present in the solution. **It is not clear why the binding of SEQ ID NO: 1 to IgE, if it even binds, would make the IgE undetectable in the system.** Since the epitope recognized by the anti-IgE antibody used by applicant is not specified, the only logical way that the peptide binding to IgE could render the IgE undetectable is if the peptide masks the epitope on IgE recognized by the anti-IgE antibody. If this is so, peptide binding does not reduce IgE levels since IgE would still be detectable if an anti-IgE polyclonal sera or an anti IgE antibody that recognizes a different epitope is used in the detection assay."

[3] "Additional data concerning the administration of a peptide consisting of SEQ ID NO: 1 can be found in Tables 3-7. The data presented was obtained by repeated measurements of just one individual, inventor Binie Lipps. **No statistical measurements were performed to demonstrate that the observed differences were significant, or that such differences could be obtained by treating a different individual.** As such, one of skill in the art would not conclude that the observed differences were due to anything more than random chance."

[4] "**The statistical significance of any of the above-described experimental data has not been provided.** As such, there is no reason that a skilled artisan would believe that the indicated effects of administration of a peptide consisting of SEQ ID NO: 1 are due to anything more than random chance, especially since there is no indication that any of the experiments were repeated. Given the doubtful nature of the guidance and working examples in the specification, **the fact that the prior art does not recognize the claimed biological properties of polypeptides comprising SEQ ID NO: 1, the fact that the prior art also does not recognize a correlation between IgE levels and diseases such as diabetes and depression**, and the general unpredictable nature of biological systems, an undue amount of experimentation would be required

to practice the claimed method of treatment.

[5] **"The examiner agrees with the applicant that the instant claims do not require any causation, diagnosis, or effectiveness in treating any human disease. However, the examiner has read the claims in light of the specification, wherein it is taught that reducing IgE levels is therapeutically beneficial in diseases such as asthma, type II diabetes, depression and autoimmunity** (see particularly the paragraph that spans pages 8 and 9). **Applicant is reminded that a method of reducing IgE levels or free IgE serum levels has no utility in and of itself.** Why would anyone want to reduce IgE unless the reduction of IgE did something, such as treat allergy? If Applicant believes that reducing IgE has a utility other than treating human disease, Applicant is invited to clearly point out where support for such a utility can be found in the specification. As was discussed in the office action mailed April 24, 205, applicant has not established that the administration of Applicant's peptide has any credible, statistically significant therapeutic benefit in the treatment of any human disease."

[6] "Applicant has also argued that the claims now recite reducing free IgE and as such the statistical significance of Applicant's data is no longer at issue. As pointed out in the office action mailed January 24, 2005, **data presented by Applicant concerning the administration of the peptide to reduce IgE, such as that in tables 3-7 is not statistically relevant. Further, in experiments 1 and 2 found on page 8 of the instant specification, administration of the peptide somehow causes the IgE not to be detected by ELISA. As discussed in the prior office action of January 24, 2005 on pages 6-8, these experiments do not prove that the peptide binds IgE. The disclosed experiments only raise the question of where has the peptide gone?** Experiment 1 is a closed system wherein saliva is mixed with either PBS or the peptide (what it is dissolved in is not specified) in a closed tube, incubated at 37°C for one hour, and they assayed for the presence of IgE. The peptide is not an enzyme and therefore it could not have degraded the IgE. It is unlikely that the presence of the peptide caused all of the IgE to precipitate from solution, since although this would effectively remove IgE from the solution to be tested for the presence of IgE, Applicant would have seen the precipitate at the bottom of the tube. IgE is significantly larger than the administered peptide, so even if the peptide does bind IGE, it could not possibly mask all epitopes present on IgE that could be bound by anti-IgE antibodies. The identity of the anti-IgE antibody used by Applicant is not disclosed, but use of a different antibody, especially polyclonal sera that recognizes multiple epitopes of IgE, would likely reveal that both samples contained the same amount of IgE. **Given that the specification does not disclose the source or identity of the anti-IgE antibody used by Applicant it is not possible for anyone to practice the claimed invention since the anti-IgE antibody used by the Applicant potentially has unique characteristics that would not be shared by all anti-IgE antibodies. Also, there is no indication that the experiments conducted by Applicant were ever repeated.** As such, the findings of Applicant;'s experiments 1 and 2 can also be quite reasonably explained as being due to random chance and not due to the effect of the peptide itself on IgE levels."

APPENDIX OF CLAIMS INVOLVED IN THE APPEAL

The text of the claims involved in the appeal are:

9. (previously amended) A method for reducing free serum IgE in a human, comprising administering to said human an effective amount of a peptide comprising at least the first four amino acids from the N-terminal of SEQ. ID. NO.: 2 to reduce serum level of free IgE in said human.

10. (previously amended) A method as in claim 9 wherein the peptide comprises the sequence of the at least first four amino acids beginning at its N-terminal and has no more than 20 amino acids total.

11. (original) A method as in claim 10 wherein the peptide is orally administered and serum IgE level is reduced.

12. (original) A method as in claim 10 wherein the range of from about 0.02 to about 200 milligrams of the peptide are orally administered on a daily basis.

13. (previously amended) A method as in claim 10 wherein in the range of from about 0.2 to about 20 milligrams of the peptide are orally administered on a daily basis and the peptide is selected from the group consisting of
SEQ. ID. NO.: 4,
SEQ. ID. NO.: 5,
SEQ. ID. NO.: 1,
SEQ. ID. NO.: 6, and
SEQ. ID. NO.: 7.

14. (previously amended) A method as in claim 10 wherein said human has an elevated serum

level of unbound IgE prior to the step of administering the peptide.

15. (previously amended) A method as in claim 14 wherein said human further has an elevated serum level of NGF, Insulin, Myoglobin and/or ADA prior to the step of administering the peptide and said elevated serum level of NGF, Insulin, Myoglobin and/or ADA is reduced following the step of administering the peptide.

16. (original) A method as in claim 14 further comprising assaying a saliva IgE level in said human.

17. (previously amended) A method as in claim 15 wherein said human further has a condition selected from the group consisting of
Asthma, Diabetes, Depression and Autoimmune Disease.

18. (previously amended) A method as in claim 17 wherein the autoimmune disease is selected from the group consisting of Systemic lupus erythematosus, Rheumatoid arthritis, Sjogren's syndrome, Reiter's syndrome, Graves' disease, Addison's disease, and Hodgkin's disease.

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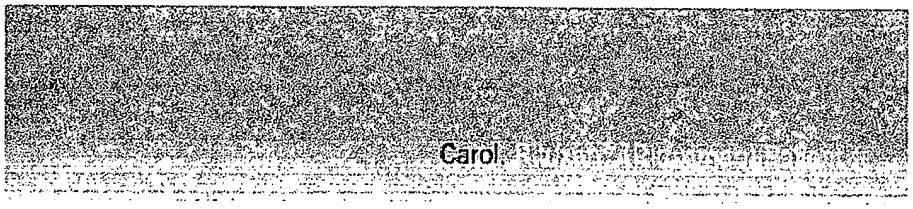

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Xolair® (Omalizumab) for Subcutaneous Use

Description

Xolair is a recombinant humanized monoclonal antibody which specifically targets the antibody IgE, an underlying component of allergic asthma. In some patients, when allergens enter the body, IgE antibodies are produced and circulate in the blood. IgE circulating in the blood binds to mast cells, which contain inflammatory chemicals (histamine, leukotrienes, others). Upon re-exposure to an allergen, IgE on the mast cell cross-links and triggers mast cells to release these chemicals. This chemical release triggers the inflammation, bronchial constriction and coughing associated with allergic asthma. Xolair is designed to bind to the circulating IgE antibodies in the blood, decreasing the amount of IgE antibodies available to bind to mast cells.

Development Status

Xolair is being evaluated in other IgE-mediated diseases. A Phase III clinical trial in pediatric asthma and a Phase II clinical trial in peanut allergy are ongoing. Xolair is being developed in collaboration with Novartis and Tanox.

Approved Uses

Xolair received U.S. Food and Drug Administration approval in June 2003 for the treatment of adults and adolescents (12 years of age and above) with moderate-to-severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. Xolair has been shown to decrease the incidence of asthma exacerbations in these patients. Safety and efficacy have not been established in other allergic conditions.

Read more about Xolair's approved use.

October 2005

Exhibit 1